The associations of social relationships with risk of incident mild cognitive impairment in older adults.

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Abstract

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Introduction: Discovering effective preventive options for dementia at earlier stages of the disease pathogenesis, such as mild cognitive impairment (MCI), is an increasingly important public health matter. Social relationships may act to prevent cognitive impairment by providing mental stimulation as well as positively influencing health behaviors and psychological processes. The objective of this study was to investigate the role of social relationships on risk of MCI in older adults.

Methods: We used data from the National Alzheimer's Coordinating Center, which maintains a set of standardized clinical data from participants that were evaluated by one of 33 National Institute on Aging funded Alzheimer's Disease Centers located across the U.S. Subjects were cognitively normal at baseline, aged 55 and older, and followed prospectively for up to 7 years for incident MCI. Social relationships, our primary exposure, included marital status (i.e., married, divorced/separated, widowed, or never married), living situation (i.e., living with spouse/partner, living with others, living alone), having children (yes, no), and having siblings (yes, no). Cox proportional regression models evaluated the association between risk

of MCI and baseline social relationships, separately, with adjustment for confounding exposures (demographics) in primary models and further adjustment for distal factors (health behaviors, e.g., smoking, alcohol abuse, substance abuse) and proximal factors (health conditions, e.g., cardiovascular disease, metabolic conditions, depression, psychiatric disorder, neurological conditions) at baseline in secondary models.

Results: The analytic sample included 4,917 subjects, followed, on average, for 3.2 years (SD=1.5), 763 of whom were diagnosed with MCI. In unadjusted analysis, MCI was associated with marital status ($p<0.001$) and living situation ($p<0.001$), but not with having children ($p=0.93$) or having siblings ($p=0.38$). However, in multivariable analyses none of the social relationships were independently associated with risk of MCI after adjusting for demographic characteristics (all $p>0.05$).

Conclusions: In contrast to previous studies, social relationships were not associated with risk of MCI after iterative adjustment for demographics, as well as health behaviors and health conditions in this analysis. Differences in results may have been due to lack of variability in exposure measures, a high rate of censoring, and/or differential drop-out across outcome status. Differences may also be due to strict entry criteria that may have better addressed the possibility of reverse causation than previous studies. Future studies that include sensitive methods and measures are needed to further investigate the potential link between social relationships and cognition. Other modifiable factors may be more strongly associated with risk of MCI and should also be investigated as possible levers for the prevention of dementia.

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Introduction

An estimated 13.9% of older adults in the U.S. have dementia.[1] In 2011, family caregivers contributed the equivalent of more than $210 billion of unpaid care and in 2012, costs of medical care services for older adults with dementia is projected to be $200 billion.[2] Dementia is clinically observable, relatively severe cognitive impairment, which may be caused by neuronal damage due to a number of diseases and conditions; often dementia results in a progressive loss of function over time.[2] Different types of dementia are associated with distinct patterns of symptoms and neuropathologies, however many people with dementia may have multiple types of neurodegenerative, vascular, or other pathologies.[2] Preventing the clinical expression of dementia resulting from these underlying pathologies is a public health priority.

Research is needed to identify effective strategies to stop the irreversible damage of dementia in the earliest stages. Social relationships have been associated with a protective effect against cognitive impairment and could play a role in preventing the accumulation of pathological changes in the brain and/or reduce the clinical impact of such abnormalities. Yet few studies have evaluated whether social relationships predict a reduced risk of mild cognitive impairment (MCI), an intermediate clinical diagnosis of early cognitive impairment thought to lie along a general continuum to dementia. The goal of this study was to investigate the associations between important social relationships and risk of any MCI in older adults that were evaluated in a clinical research setting.

Pathological changes may begin to occur years and even decades before clinical symptoms of dementia,[3] so it is thought that interventions may be more effective earlier in the disease course when some damage to the brain may still be prevented. Subsequently, the diagnostic category MCI was developed to describe the intermediate clinical stage between cognitive changes of normal aging and dementia.[4] Patients with MCI have substantial

cognitive decline over time, but do not yet have functional impairment.[4] Although, some patients with MCI remain stable or their cognition improves, MCI is more often a prodromal stage of brain disease that leads to dementia.[5] MCI is most commonly the initial clinical expression for Alzheimer's disease (AD), and can be classified as MCI due to AD;[6] however MCI is a heterogeneous category and can represent other diseases that cause dementia.[5] Identifying modifiable risk factors for expression of MCI may help generate intervention strategies that may broadly prevent the development and progression of MCI to dementia.

One strategy proposed to help older adults maintain cognitive function and prevent dementia has been to improve aspects of an individual's social environment.[7,8] There is a growing body of evidence suggesting that both the quality and quantity of social relationships are associated with better cognitive outcomes in the elderly.[9–30] Previous studies provide evidence that, in general, important social relationships, such as being married and living with someone, are associated with lower risk of developing dementia [11,16,21] and with slower rates of cognitive decline[20,22,25,26] independent of perceived quality of the relationship, demographics, and health status. On the other hand, loss of important relationships, such as bereavement by a spouse, has in some cases been associated with increased risk for cognitive decline, comparable or more than that of never being married.[20,25] See Appendix A for a detailed table outlining methods and results from studies published between 1999 and 2012.

However, there is a worry that the prior observed associations are instead due to early clinical changes acting to negatively influence social relationships (reverse causation) because many studies have had relatively short follow-up periods[11,13,16,21,22] or used insensitive measures of cognition that may not identify all affected subjects at baseline.[11,19,24,25] Several studies have failed to find longitudinal associations between social relationships and cognitive impairment.[12,17,23,30] Therefore, it may be important to use sensitive cognitive measures when determining subject eligibility in order to exclude subjects

with subtle cognitive impairments from entering the study; and studies with shorter follow-up times should study outcomes that mark early stages of cognitive impairment such as MCI.

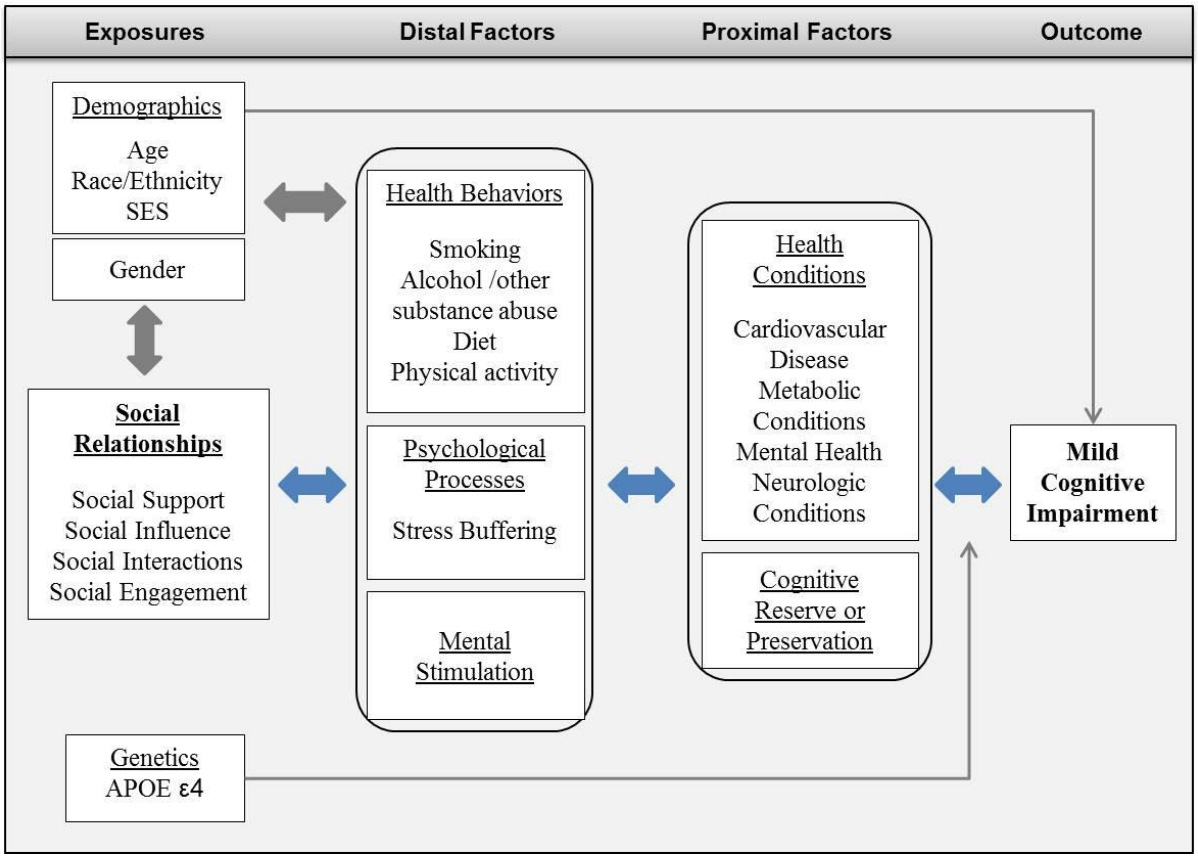
Furthermore, to create social relationship summary measures marital status is often included but subjects are usually lumped into dichotomous categories based on current marital status; yet there is evidence that the risk of dementia associated with being widowed, divorced/separated, or never married may differ in magnitude and in causal mechanisms.[25,29] Although, one recent study found that previously married subjects but not never married subjects were at higher risk of any MCI compared to married subjects[29] these results were part of secondary analysis and need to be replicated. To our knowledge no studies have extensively evaluated the role of a variety of important social relationships with risk of MCI. Such research could help identify specific at-risk subgroups and inform the development of preventive strategies.

Conceptual Model

Figure 1 links social relationships, as well as other exposures, to MCI through distal and proximal mechanisms that may influence the pathogenesis of dementia or the clinical expression of the disease. Demographics (confounding exposures), such as age, race/ethnicity, socioeconomic status (SES) and gender may have a role in determining social relationships[31,32] and in influencing the development of MCI through distal mechanisms,[26,29] potentially confounding the associations of interest. Genetics (modifying exposures), such as apolipoprotein E (APOE), are strong predictors of MCI,[5] contributing to neuropathological changes and may modify the influence of social relationships on risk of MCI.[25]

Social relationships, the primary exposure, provide opportunities for social influence and social interaction, which feed into distal factors in several ways.[31,32] For instance, social relationships can either encourage or discourage health behaviors like exercise, diet, smoking status, substance abuse, adherence to medicine, and access to health care resources.[33]

Similarly, social relationships can affect psychological processes to either buffer or heighten stress, depending on whether the social relationships are positive or negative, respectively.[32,34] Finally, social relationships can affect the extent to which an individual is mentally stimulated, which may benefit neuronal processes and cognitive functioning.[12]



Note: Primary pathway is illustrated with blue arrows.

Figure 1. Conceptual model of how social relationships are hypothesized to affect development of mild cognitive impairment (MCI).

These distal factors, then, influence proximal factors. For instance, health behaviors and psychological processes influence physiology such as cardiovascular reactivity, neuroendocrine function and immune response, which can impact proximal mechanisms, such as health conditions (e.g., cardiovascular disease, metabolic factors, mental health, or neurological conditions).[35–37] Vascular disease and metabolic factors, such as hypertension, hypercholesterolemia, and diabetes may directly contribute to neuropathological changes in the dementia process.[38] Depression, psychological stress, and neurological conditions, such as traumatic brain injury, have also been linked to an increased risk of cognitive impairment,[39–

[41] however, depression may also represent incipient dementia.[42] Mental stimulation on the other hand, may help preserve cognitive functioning in normal aging (i.e. "use it or lose it") and may modify the clinical expression of brain pathology, through "cognitive reserve".[43]

Gender may also play an important role in determining the nature of social relationships such that there may gender-specific effects when evaluating associations.[44] Men and women have differing patterns of social relationships: women tend to have a wider range of sources of emotional support than men, while men tend to report more practical support from their closest relationships, usually their spouse.[44]

The relative importance of each of the described pathways may differ depending on the underlying disease process that leads to MCI. However, taking a life course approach[45] to understanding development of MCI, we hypothesize that, over the life-span, social relationships act simultaneously through these pathways to influence risk of MCI. The primary objective of this study was to evaluate the associations between important social relationships and risk of incident MCI in cognitively normal older adults that were evaluated by one of the National Institute on Aging's (NIA) Alzheimer's Disease Centers (ADCs).

We hypothesized that participants who reported having social relationships would have a lower risk of MCI than those who reported not having social relationships. Further, because previous research suggests there are gender-specific effects of social relationships on overall health status[44] and cognitive decline, specifically,[16] a secondary purpose of this study was to assess whether associations between social relationships and risk of MCI would be different for men and women. Finally, because research also suggests that genetic predisposition to dementia may modify the effect of social relationships on risk of MCI,[25] we also investigated the interaction between social relationships and having the major genetic risk factor for late-onset Alzheimer's disease (the APOE ε4 allele).[46]

Methods

Study setting

Data was obtained from the National Alzheimer's Coordinating Center (NACC) which maintains a database of standardized clinical data, the Uniform Data Set (UDS),[47,48] from participants with and without dementia that were evaluated by one of 31 Alzheimer's Disease Centers (ADCs) throughout the U.S.A. Each ADC operates independently—recruiting and enrolling subjects according to their own protocols; subjects are generally volunteers that responded to recruiting efforts (i.e. ADC or non-ADC association media appeals, clinic- or community-based sampling mechanisms) primarily to participate in a research study or were referred to the ADC by a clinician, friend, relative, or themselves due to concerns about their health, cognition, or behavior.

All subjects received an initial clinical evaluation and up to 7 follow-up evaluations; data are collected on an annual basis.[47,48] The UDS contains information on the clinical, neuropsychological, and diagnostic results of evaluations; methods and rationale for the UDS has been previously published.[48] NACC conducts ongoing data quality assurance procedures to ensure that UDS data is accurate and that diagnoses fit current diagnostic standards.

Study sample

The analytic sample was comprised of subjects who were evaluated with the UDS and had data entered into the NACC database between September, 2005 and June, 2012. Subjects included in the NACC UDS database were be eligible for this analysis if they were aged 55 years and older at initial visit and had "normal" cognition. Due to the long prodromal phase of neurodegenerative dementias,[49] it is likely that some eligible subjects already had neuropathology, however, we attempted to reduce the number of subjects experiencing cognitive symptoms by restricting the criteria for normal cognition to subjects that were defined cognitively normal based on clinician assessment and scored within the normal range

on both the Clinical Dementia Rating[50] (CDR; global score=0) and Mini-Mental State Examination[51] (MMSE; score >26). Only subjects with complete (no missing or unknown) information on all measures were included.

Assessments

UDS data was collected from trained clinicians or interviewers through in-person office visits at each ADC. Research subjects were asked to attend the evaluation with a knowledgeable informant (usually a family member or friend) to provide information on changes in subject cognitive and functional abilities from previous levels.[52] Data were recorded by clinicians or interviewers directly on UDS forms (electronic or hard copy). At each visit, information on subject socio-demographic characteristics, subject family history, presence and severity of behavioral symptoms, and level of functional impairment were collected via structured interviews with the subject and their informant. Information on medical history was obtained through medical records, subject and/or informant interview and observations, as needed. Finally, subjects received physical and neurological examinations, as well as a battery of neuropsychological assessments, at each visit. Subject death or drop-out from the study was also documented.

Social relationships were assessed via structured interview and included marital status, living situation, number of children, and number of siblings. Marital status was recorded as married, widowed, divorced, separated, never married, living as married, other, or unknown. Living situation was recorded as the subject lives alone, lives with spouse or partner, lives with a relative or friend, lives with group, other, or unknown. The number of biological children and number of full siblings (living or deceased) was recorded with family history. Further information on date of birth, vital status, year of death if deceased, and dementia history was gathered only after February 2008. Frequency of contact and quality of relationships were not assessed in the UDS.

Diagnoses of MCI were made at all ADCs by either a single clinician or consensus group of clinicians, after a review of all evaluation information available. The diagnosis was established according to published criteria,[53] where a subject was determined to have MCI if they had complaints about their cognition, their cognition was not normal for their age, and they had recent cognitive decline but they had essentially normal functional activities and did not meet criteria for dementia diagnosis. Subjects were further classified based on clinical judgment and/or neuropsychological tests as having "amnestic" MCI (aMCI) if memory impairment was present or "non-amnestic" MCI (naMCI) if there was no memory impairment. Subjects were also classified as having single-domain or multiple-domain MCI if one or multiple cognitive domains (e.g., memory, executive function, language) were impaired, respectively.[53]

Demographic factors were assessed via structured interview and included age, years of education, sex (male, female), race, and ethnicity (Hispanic, non-Hispanic). Race was recorded as White, Black or African America, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, other, and unknown.

Trained ADC clinicians assessed history of health behaviors, including smoking, alcohol abuse, and other substance abuse based on subject or informant report, medical records and/or observation. Cigarette smoking history (yes, no, unknown) was assessed by asking the clinician the question: "Has the subject smoked more than 100 cigarettes in her/his life?" Alcohol and other substance abuse were assessed by asking for the clinician's best judgment about whether the subject had experienced significant impairment in work, driving, legal or social areas that occurred over a 12-month period due to alcohol or other substance use, each. Responses for each alcohol and other substance use were recorded as absent, recent/active, remote/inactive, or unknown.

Clinicians also assessed a series of health conditions, including cardiovascular diseases

(heart attack, atrial fibrillation, angioplasty, cardiac bypass procedure, pacemaker, and congestive heart failure), metabolic conditions (hypertension, hypercholesterolemia, diabetes, B12 deficiency, thyroid disease, and incontinence), depression, other psychiatric conditions, and neurological conditions (seizures or traumatic brain injury), which were determined according to the clinician's best judgment based on subject/informant report, medical records, and/or observation. Subject history for each condition was recorded as absent, recent/active, remote/inactive, or unknown, with the exception of depression, which was recorded as active within the past 2 years (yes, no, unknown) and as episodes prior to 2 years (yes, no, unknown). Based on each ADC's protocol and subject preference, APOE genotyping was conducted for a select sample of subjects and genotype information was linked to the UDS; APOE genotype (one of six combinations of ε2, ε3, and ε4 alleles) was recorded if known and otherwise was recorded as missing/unknown/not assessed.

Analytic Measures

Primary Exposure: Social Relationships

Baseline measures of social relationships were used to derive four primary measures, including marital status, living situation, having children, and having siblings. Marital status was defined as a four-category indicator variable: married or living as married (reference), widowed, divorced/separated, or never married. Living situation was defined as living with spouse (reference), living with others (i.e. living with relatives or living in a group), or living alone. Having children was defined as having at least one biological child, living or deceased, (reference) or none, having siblings was defined similarly. Information on child or sibling vital status was not assessed for all subjects and so it was not incorporated into our measures.

Primary Outcome: Mild Cognitive Impairment

MCI was defined as a diagnosis of *any* type of MCI: amnestic or non-amnestic, single or multiple domain.

Covariates

Covariate selection was guided by our conceptual model (Figure 1), as well as availability of data. Available baseline measures of confounding exposures (demographic characteristics), distal (health behaviors), and proximal (health conditions) factors were used in this analysis. Demographic characteristics included sex, age (categorized in as aged 55-64 years, 65-74 years, 75-84 years, or 85+ years), education (categorized as 0-12 years; 13-15 years, or 16+ years), race/ethnicity (categorized as Caucasian- Non-Hispanic, Caucasian-Hispanic, Black-Non-Hispanic, Black -Hispanic, Other- Non-Hispanic, or Other- Hispanic). Available health behaviors included dichotomous measures of smoking status (current/previous smoker vs. never smoker), alcohol abuse (current/previous alcohol abuse vs. none), and other substance abuse (current/pervious other substance abuse vs. none). Health conditions included individual dichotomous measures indicating presence/history or absence of any cardiovascular disease, metabolic condition, depression, psychiatric disorder, and neurological condition. Presence or history of a condition was considered for conditions documented as recent/active or remote/inactive, while absence was considered for conditions documented and absent. In addition, APOE ε4 allele status (modifying exposure) was defined as having at least one ε4 allele or none.

Statistical analyses

All subjects were considered at risk for incident MCI at baseline. No biomarker data were available to estimate who may or may not have had asymptomatic pathology. As used in a prior study,[29] the onset of MCI was estimated as the midpoint between the last cognitively normal evaluation and the first-ever evaluation with a diagnosis of any MCI. Subjects who developed dementia without a previous diagnosis of MCI were assumed to have passed through an MCI stage with onset at the midpoint between the last visit with a normal evaluation and first visit with dementia diagnosis. Subjects that did not develop MCI were

censored at their date of death, date of discontinued participation, or last clinical evaluation, as applicable. Our analyses assessed time to first ever clinical MCI diagnosis as reported in the UDS.

Descriptive statistics determined subject characteristics according to the entire sample and stratified by clinical outcome (did not develop MCI, developed MCI). Descriptive statistics on subject characteristics stratified by marital status and by living situation were also explored. Continuous measures were compared with independent-sample *t* tests and categorical measures were compared with χ^2 tests. We examined Kaplan-Meier graphs to visualize unadjusted differences in probability of survival of MCI according to social relationship measures and compared survival functions within each social relationship with log-rank tests.

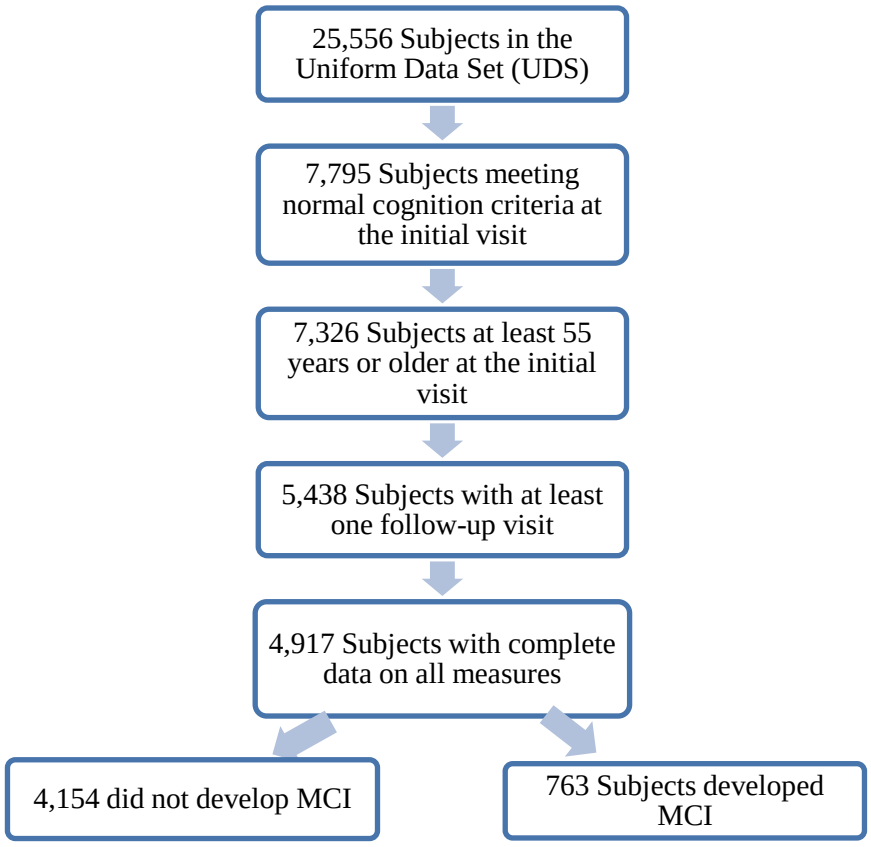
We used multivariable Cox proportional hazard models with years of follow-up as the time scale to evaluate the associations between social relationships and risk of developing MCI, separately (hazard ratios [HR], 95% Confidence Interval [CI]). Use of age as the time scale was considered, however, years since initial visit was chosen due to concerns that models using age as the time scale change interpretation of models from risk of MCI over follow-up to comparing age-of-onset of MCI and that the latter should include adjustment for other age-of-onset factors, which may not be accurately collected in the UDS. Models included clustering by ADC to account for potential correlation in diagnoses within the same center. Associations between MCI and social relationships were assessed separately for each social relationship measure.

Primary models were adjusted for confounding exposures according to our conceptual model and previous studies. Secondary models were adjusted additionally for available proximal (health behaviors) and distal factors (health conditions) at baseline to assess the association of social relationships and MCI, since proximal and distal factors may have

influenced baseline social relationships and thus may potentially act as a confounder (vs. a mediator). A step-wise modeling approach was taken for adjustment of covariates due to the fact that proximal and distal factors are potential confounders but are also in the causal pathway. Next, we assessed whether the association between social relationships and risk of MCI varied based on (or was modified by) gender or APOE ε4 allele status. To do this, we included multiplicative interaction terms (gender X social relationship and APOE allele X social relationship) in models assessing the association between each measure of social support and risk of MCI. Interaction models were also fit using a stepped approach with primary models adjusted for demographics and secondary models also including health behaviors and health conditions. Proportional hazards assumptions were assessed and satisfied analytically by testing Schoenfeld residuals and graphically (Kaplan-Meier and log-log plots). Statistical analyses were performed using STATA 12.0. All tests were two-tailed with α -levels set to 0.05.

Results

The final analytic sample was comprised of 4,917 subjects, among whom there were 763 cases of incident MCI during follow-up (Figure 1). On average, subjects were followed for 3.2 years after the initial visit (SD=1.5) and the study sample contributed about 15,439 person-years of follow-up. The vast majority (92.4%) of subjects came to the ADC as a volunteer to participate in a research study; 40.6% of subjects were referred by themselves, a relative, or friend; 11.4% were referred by a clinician; 22.2% responded to ADC or non-ADC solicitation/recruitment; and the rest (25.9%) were recruited or referred through other mechanisms. Subjects were a majority female (66.6%) and non-Hispanic Caucasian (78.8%), while the mean age was 73.3 (SD=8.7) and mean years of education was 15.5 (SD= 2.9).



Abbreviations: MCI, Mild Cognitive Impairment; NACC, National Alzheimer's Coordinating Center; UDS, Uniform Data Set.

Figure 2. Study sample flow chart.

Table 1. Subject characteristics at baseline.

Characteristic	No MCI (n=4,154)	Any MCI (n=763)	Total (n=4,917)	P-value*
Demographics	N(%) unless otherwise noted			
Age (yrs)				<0.001
55-64	753 (18.1)	49 (6.4)	802 (16.3)	
65-74	1,777 (42.8)	205 (26.9)	1,982 (40.3)	
75-84	1,258 (30.3)	309 (40.5)	1,567 (31.9)	
85+	366 (8.8)	200 (26.2)	566 (11.5)	
Female	2,795 (67.3)	481 (63.0)	3,276 (66.6)	0.02
Race				0.02
Caucasian- Non-Hispanic	3,235 (77.9)	639 (83.8)	3,874 (78.8)	
Caucasian- Hispanic	157 (3.8)	23 (3.0)	180 (3.7)	
Black-Non-Hispanic	655 (15.8)	89 (11.7)	744 (15.1)	
Black -Hispanic	13 (<1)	2 (<1)	15 (<1)	
Other- Non-Hispanic	74 (1.8)	7 (<1)	81 (1.7)	
Other- Hispanic	20 (<1)	3 (<1)	23 (<1)	
Education (yrs)				0.002
0-12	823 (19.8)	177 (23.2)	1,000 (20.3)	
13-15	1,804 (43.4)	355 (46.5)	2,159 (43.9)	
16+	1,527 (36.8)	231 (30.3)	1,758 (35.8)	
Reason for coming to ADC				0.03
Participate in a research study	3,839 (92.4)	685 (89.8)	4,524 (92.0)	
Clinical Evaluation	271(6.5)	70 (9.2)	341 (6.9)	
Other/Unknown	44 (1.1)	8 (1.1)	52 (1.1)	
Health Behaviors (current or previous)				
Smoking				0.09
Yes	1,915 (46.1)	326 (42.7)	2,241 (45.6)	
Alcohol abuse				0.09
Yes	128 (3.1)	15 (2.0)	143 (2.9)	
Substance abuse				0.02
Yes	42 (1)	1 (<1)	43 (<1)	
Health Conditions (present or past history)				
Cardiovascular disease[a]				<0.001
Yes	977 (23.5)	248 (32.5)	1,225 (24.9)	
Metabolic condition[b]				0.24
Yes	3,236 (77.9)	609 (79.8)	3,845 (78.2)	
Depression				0.54
Yes	890 (21.4)	171 (22.4)	1,061 (21.6)	
Psychiatric condition				0.40
Yes	139 (3.4)	21 (2.8)	160 (3.3)	
Neurological condition[c]				0.95
Yes	519 (12.5)	96 (12.6)	615 (12.5)	
APOE ε4 allele**				0.002
Yes	831 (27.4)	189 (33.9)	1,020 (28.4)	
Cognitive Impairment				
CDR-SB, mean (SD)	0.011 (0.075)	0.033 (0.140)	0.015 (0.088)	<0.001

Table 1. continued

Social Relationships				
Marital Status				<0.001
Married	2,479 (59.7)	412 (54.0)	2,891 (58.8)	
Widowed	905 (21.8)	237 (31.1)	1,142 (23.2)	
Divorced/Separated	540 (13.0)	76 (10.0)	616 (12.5)	
Never Married	230 (5.5)	38 (5.0)	268 (5.5)	
Living Situation				<0.001
Living with spouse	2,440 (58.7)	394 (51.6)	2,834 (57.6)	
Living with others	265 (6.4)	72 (9.4)	337 (6.9)	
Living alone	1,449 (34.9)	297 (38.9)	1,746 (35.5)	
Children				0.55
Yes	3,470 (83.5)	644(84.4)	4,114 (83.7)	
No	684 (16.5)	119 (15.6)	803 (16.3)	
Siblings				0.48
Yes	3,669 (88.3)	667 (87.4)	4,336 (88.2)	
No	485 (11.7)	96 (126)	581 (11.8)	

[a] Heart attack, atrial fibrillation, angioplasty, cardiac bypass procedure, pacemaker, heart failure, or other.
[b] Diabetes, hypertension, hypercholesterolemia, B12 deficiency, thyroid disease, or incontinence.
[c] Seizures or traumatic brain injury
CDR-SB, Clinical Dementia Rating sum of boxes (range of 0-18, higher signifies more cognitive impairment).
*Calculated using Pearson chi-square test (categorical measures) or Student's t-test (continuous measures)
**Only assessed for 3586 (72.9%) of subjects.

Table 1 describes subject baseline characteristics overall and stratified by MCI outcome. Subjects that developed MCI tended to be slightly older, a higher proportion were men, non-Hispanic Caucasians, and less educated; plus they had relatively more cardiovascular disease, slightly less depression or psychiatric conditions, less substance abuse, and a higher proportion had at least one APOE ε4 allele among those that had APOE tested (Table 1). A higher proportion of subjects that developed MCI were referred to the ADC because of concerns about the subject's health or cognition. There was a significant difference (all $p < 0.05$) for age, sex, race/ethnicity, education, reason for coming to the ADC, cardiovascular disease, APOE ε4 allele status, and cognitive impairment at baseline between subjects that did and did not develop MCI during follow-up.

The distribution of baseline social relationships is also shown in Table 1. To summarize, at baseline, approximately 60% of subjects were married and lived with their spouse or partner. Very few subjects were never married (5.5%) or living with others than their spouse or partner (6.9%) at baseline. The vast majority of subjects had at least one child (83.7%) and

at least one sibling (88.2%). There were substantial differences in demographic and health characteristics according to marital status (Appendix B) and living situation (Appendix C). In general, married subjects were more often Caucasian men and tended to have fewer health behaviors and health conditions than widowed, divorced/separated, or never married subjects ($p<0.05$). Widowed subjects also tended to be older, less educated, more cognitively impaired than married, divorced/separated, and never married subjects ($p<0.05$). Subjects that lived with others (not their spouse) or alone were more likely to be women, older, a minority, less educated, have health conditions, and worse cognitive impairment than subjects that lived with their spouse/partner (for all, $p<0.05$).

Total number of MCI events and the unadjusted incidence rate of MCI for each social relationship are shown in Table 2. The overall incidence of MCI was 49.4 per 1,000 person-years; however, rates were higher among subjects that, at baseline, were widowed, living with others or living alone, or had no siblings.

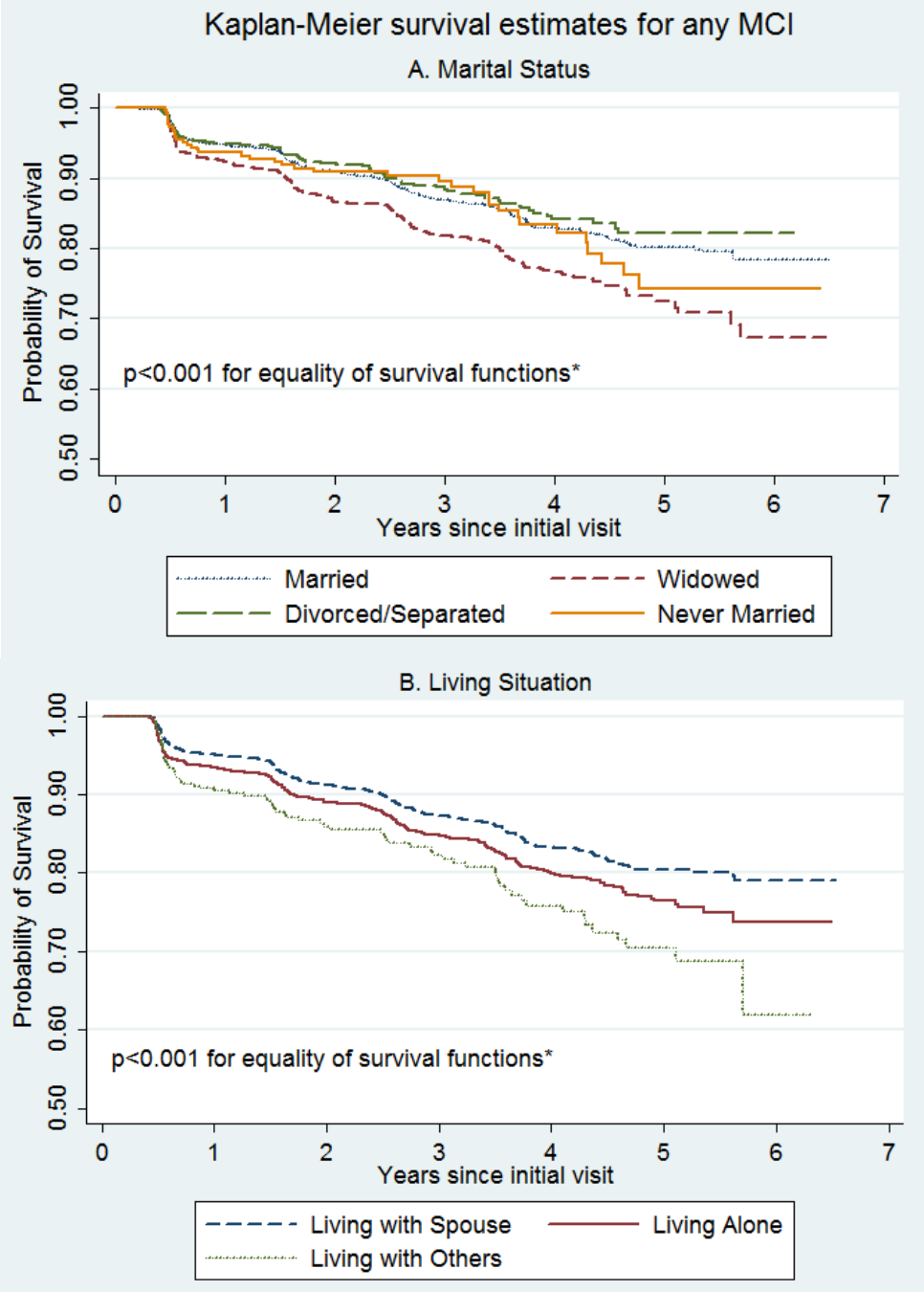
Table 2. Social relationships at baseline and MCI events among subjects (n=4,917).

Characteristic	Persons at risk	Person- years of follow up	MCI events	Incidence rate per 1,000 (95%CI)	
Marital Status					
Married	2,891	9,187	412	44.8	(40.7, 49.4)
Widowed	1,142	3,593	237	66.0	(58.1, 74.9)
Divorced/Separated	616	1,888	76	40.2	(32.1, 50.4)
Never Married	268	771	38	49.3	(35.9, 67.8)
Living Situation					
Living with spouse	2,834	9,011	394	43.7	(39.6, 48.3)
Living with others	1,746	1,007	297	54.8	(48.9, 61.4)
Living alone	337	5,421	72	71.5	(56.8, 90.1)
Children					
Yes	4,114	13,022	644	49.5	(45.8, 53.4)
No	803	2,417	119	49.2	(41.1, 58.9)
Siblings					
Yes	4,336	13,661	667	48.8	(45.3, 52.7)
No	96	1,778	96	54.0	(44.2, 65.9)

MCI, Mild cognitive impairment

Kaplan-Meier survival estimates showing the estimated probability of not developing MCI over the follow-up period are illustrated in Figure 3 according to marital status and

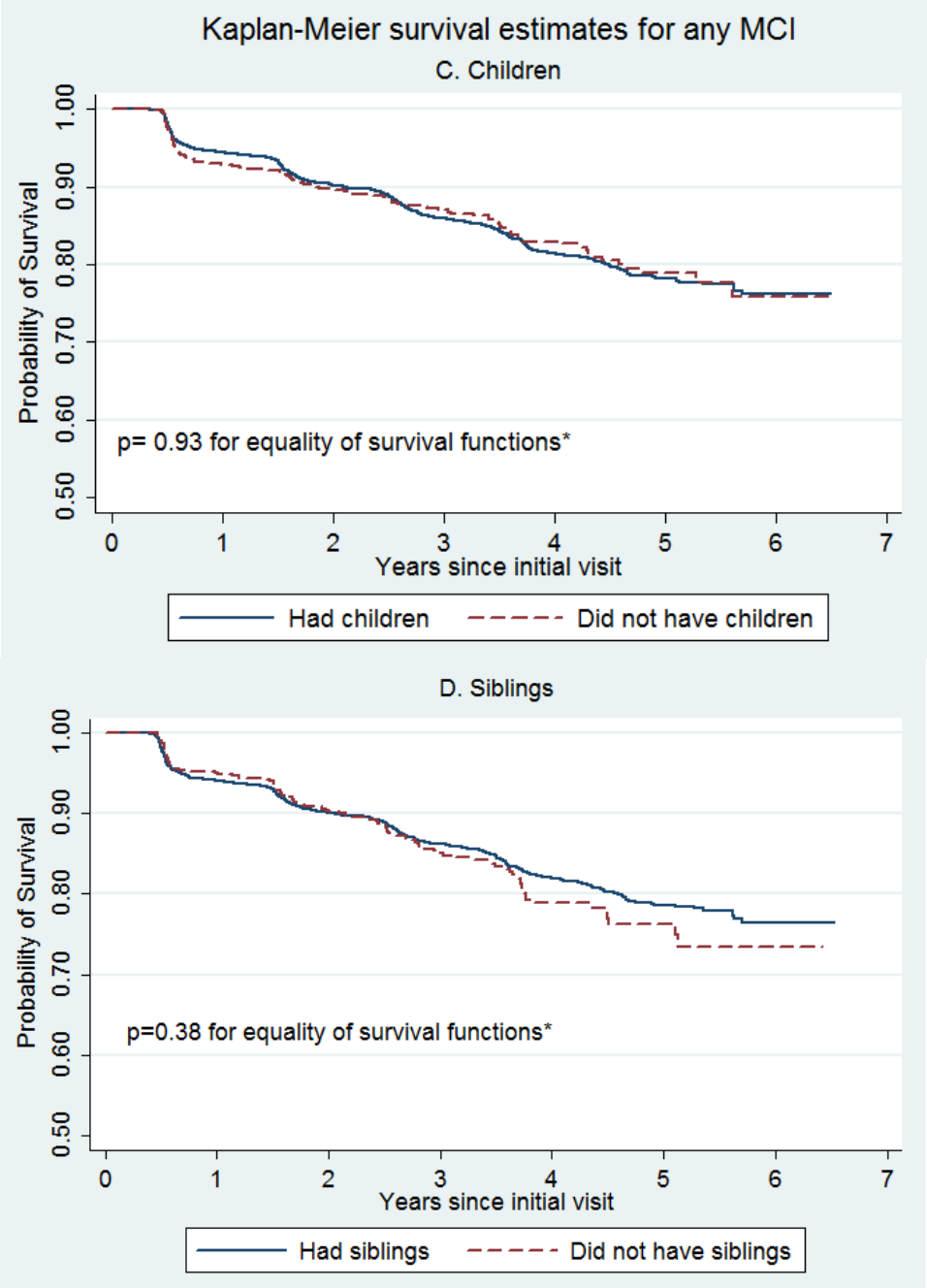
living situation and in Figure 4 for having children and having siblings. Overall, survival functions were significantly different for marital status and living situation (both, p<0.001).



Note: Graphs show only 50-100% survival.
MCI, Mild cognitive impairment
*Calculated using log-rank test

Figure 3. Kaplan-Meier survival estimates for risk of MCI by subject (A.) marital status and (B.) living situation at baseline (n=4,917)

There were no significant differences in survival function for having children or having siblings (both, p>0.05).



Note: Graphs show only 50-100% survival.
MCI, Mild cognitive impairment
*Calculated using log-rank test

Figure 4. Kaplan-Meier survival estimates for risk of MCI by whether the subject (C.) had children and (D.) had siblings (living/deceased) at baseline (n=4,917)

Adjusted hazard ratios and 95% confidence intervals are presented in Table 3 for the primary models. After adjustment for demographic characteristics, there was no evidence for an association between risk of MCI and marital status, living situation, having kids or having siblings (all p-values>0.05). Results were similar after additional adjustment for health

behaviors and health conditions (all models p>0.05; data not shown). There was no significant interaction between any measure of social relationships and gender (all models p>0.05). Among the subset of subjects with APOE ε4 allele information (n= 3,586) there was no significant interaction between any measure of social relationships and having an APOE ε4 allele (all models p>0.05).

Because associations observed between risk of MCI and both marital status and living situation in unadjusted models disappeared after adjustment for demographic characteristics, and because age is strongly associated with both social relationships and risk of MCI, we conducted post-hoc secondary analyses to investigate whether age was the primary driving factor behind the unadjusted associations. Indeed, after adjustment for age alone, marital status and living situation were not significantly associated with risk of MCI (both p-values >0.05) and model estimates (data not shown) were very similar to those resulting from the primary model found in Table 3.

Table 3. Adjusted association between risk of MCI and social relationships (n=4,917).**

Social Relationship	Person- years of follow up	MCI Events	Hazard ratio	(95% CI)	P-value
Marital Status					0.37*
Married	9,187	412	1.00	---	
Widowed	3,593	237	0.86	(0.71, 1.04)	
Divorced/Separated	1,888	76	0.95	(0.72, 1.25)	
Never Married	771	38	1.14	(0.83, 1.55)	
Living Situation					0.11*
Living with spouse	9,011	394	1.00	---	
Living with others	1,007	297	0.92	(0.77, 1.10)	
Living alone	5,421	72	1.30	(0.93, 1.80)	
Children					0.36
Yes	13,022	644	1.00	---	
No	2,417	119	1.09	(0.90, 1.33)	
Siblings					0.61
Yes	13,661	667	1.00	---	
No	1,778	96	1.06	(0.84, 1.35)	

** Model adjusted for age, sex, education, race, and Hispanic ethnicity
MCI, Mild Cognitive Impairment
*Overall p-value calculated with Wald test

Discussion

We investigated the individual associations between risk of MCI and four types of important social relationships (being married, living with others, having children and having siblings) in older adults using a large multi-center clinical research dataset. Although, we found crude differences in risk of MCI according to baseline marital status and living situation, we did not find an association between having children or having siblings and risk of MCI. Furthermore, after iterative adjustment for demographics alone as well as demographics, health behaviors, and health conditions, there was no evidence for an association between risk of MCI and any of the four social relationships. There were no significant interactions between social relationships and gender or having an APOE ε4 allele.

Our results suggest that social relationships were not related to risk of MCI in our sample. However, it may be that our measures of social relationships and MCI were not sensitive or variable enough in this sample to detect an association after adjustment for strong predictors such as demographics, especially age. More research may be needed to confirm that no association exists between social relationships and risk of MCI prior to deciding that enhancing social relationships should not be a focus of interventions to prevent dementia. Nevertheless, simultaneous research should investigate other potentially important modifiable risk factors for dementia, such as education, depression, and cardiovascular risk factors.

These results are consistent with a few studies that found no evidence for a longitudinal association between having social relationships and cognitive functioning, independent of potential confounders.[12,17,23,28,30] Most of these studies used general measures of cognition as the outcome. As such, our study extends these findings to risk of MCI, a pre-dementia based clinical diagnosis. However, our results are unexpected because they are inconsistent with much of the research literature. Many studies have found associations of marital status and living situation with cognitive outcomes that remain robust after adjustment for

demographics, health behaviors, and health conditions.[11,20,25,26,29]

Positive findings in some prior studies may instead be due to reverse causation; individuals with good cognition may retain social relationships over time compared to subjects with poor or declining cognitioning.[13] When reverse causation is better accounted for, results are less consistent, with some studies still finding associations between social relationships and cognition with follow-up of more than 10 years[20,25,26] and another that did not find such associations after excluding subjects who developed dementia during their 20 year follow-up.[28] Our study improved upon many prior studies by using strict entry criteria to try to eliminate subjects with subtle cognitive deficits that may have influenced their social relationships prior to study enrollment. Nevertheless, there is some indication that reverse causation was still possible in our sample; because, despite our entry criteria, subjects that developed MCI during follow-up were more likely to come to the ADC for a clinical evaluation and, on average, had worse cognition than subjects that did not develop MCI.

Strengths and Limitations

This study is the first large multi-center prospective studies of the associations between multiple important social relationships and risk of MCI, a clinical diagnosis of early cognitive changes that may reflect a state at which interventions may still be effective at slowing disease progression and preventing dementia. Other strengths of our study included using definitions of marital status and living situation that allowed for potential differences between subjects who underwent the potential psychological distress of bereavement and those that were just never married. Finally, as mentioned above, we restricted to subjects with cognitive test scores in the normal range to prevent potential for reverse causation to have occurred in our sample. In addition, it is unlikely that marital status and nearly impossible that having children and having siblings were affected by a subject's cognitive decline.

There are several important limitations in this study. First, this sample was a cohort of

clinical research subjects with normal cognition that were most often volunteers or referred to the ADC for clinical evaluation. Subjects may have been motivated to participate in research due to high education level or to family history of dementia or other risk factors. Thus our results may not be generalizable to the U.S. population. Prior studies with positive findings differed primarily from ours by involving population-based samples of community dwelling older adults.[11,20,25,26,29] Furthermore, an individual's social relationship status may have influenced enrollment in the UDS. For instance, subjects may be more likely to participate if they had more social relationships, possibly because of pressure and encouragement from family or friends. There were very few subjects that had never been married, or did not have children or siblings in our sample. Little variation in these measures may have limited power to detect an association.

Second, our results may have been biased if there were differential drop-out or follow-up of subjects. Subjects with social relationships may be more likely than those without to have been followed for longer (and have more time to develop MCI) or return for a visit if symptomatic. Meanwhile, socially isolated subjects may be more likely to drop out when beginning to develop cognitive problems, perhaps due to lack of assistance with scheduling and transportation to the evaluation. Consequently, risk of MCI could be estimated in our study as falsely high among subjects with social relationships, which could cancel out the additional risk associated with social isolation, if any.

Third, we used crude measures of social relationship that did not differentiate between positive and negative social relationships and did not assess quality, quantity, or frequency of contact of relationships. We also did not account for changes in social relationships during follow-up. Both these issues could have resulted in misclassification error that would bias our estimates towards the null. However, we used baseline social relationships to limit the possibility of reverse causation, although due to the long prodromal stage of some dementias

some potential for reverse causation remains.

Other limitations included short follow-up period and substantial censoring in the data. On average, subjects were only followed for 3 years and with follow-up extending to 7 years, censoring especially in the later years of follow-up may have severely limited the power of our study to detect differences using survival analysis. We attempted to maximize power by assessing risk of any MCI, however, clinical presentation of MCI is heterogeneous; and recent research on incident MCI suggests that risk factors for may differ depending on MCI subtype, so analyses that pool aMCI and naMCI may fail to identify relevant risk factors.[29]

More research is needed to better understand whether social relationships are associated with risk of MCI, or other early-stage cognitive impairment. Future studies should recruit from diverse populations that have variability in social relationships, and take an active role in preventing loss to follow-up (e.g. through home visits, or providing transportation if needed). Studies should also use measures that integrate information on quality and quantity of social relationships, because they are stronger predictors of mortality than basic relationships,[54] and may be more able to detect associations. Further efforts to use more sensitive analytic tools should be attempted. Several studies on early cognitive changes have found associations by incorporating repeated measures of cognition over time to detect even slight changes in cognition.[20,26] Longitudinal methods of continuous measures that can detect early changes in cognition may be more sensitive than survival analysis to detect an association, while still focusing on early-stage cognitive impairment.

Conclusion

In conclusion we did not find evidence to support the hypothesis that social relationships were associated with risk of MCI after adjustment for important confounders. Rather our results suggest that demographic factors mostly account for observed unadjusted differences between social relationships and development of MCI. Prior to deciding that enhancing social

relationships should not be a focus of interventions to prevent dementia more research may be needed to confirm that no association exists between risk of MCI and social relationships. More longitudinal research should use sensitive measures to assess whether the quality or quantity of social relationships can predict future cognitive impairment among cognitively normal older adults. Concurrent research efforts should assess whether other potentially important modifiable risk factors for dementia are also associated with risk of MCI. Identifying other potentially modifiable factors could help find alternative strategies to prevent MCI and progression to dementia.

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Appendix A

Table 4. Literature review- social relationships and cognitive functioning

Longitudinal Studies from 1999-2012								
Study, Country	**Year**	**N**	**Age**	**Exposure**	**Follow -up**	**Outcome**	**Cognitive assessment**	**Resulting associations**
Bassuk et al,[9] USA	1999	2,812	>65	Social engagement index (marital status, contacts, attendance of church, recreational activities)	3,6, 12	Incident cognitive decline	Global cognitive functioning	Social disengagement with cognitive decline
Hultsch et al,[10] Canada	1999	250	58-65	Social activities; new-information-processing activities; physical activity	6	Decline in cognitive functioning	Memory, comprehension, and speed	No association of "Active lifestyle" with cognition
Fratiglioni et al,[11] Sweden	2000	1,203	75+	Social network: individual items and composite	3	Incident dementia	Diagnostic and Statistical Manual of Mental Disorders	limited social network with increased risk of dementia
Seeman et al,[12] USA	2001	1,189	70-79	Social ties; emotional support; instrumental support	7.5	Overall cognitive function	Neuropsychological battery	Emotional support (but not social ties) with better cognitive function
Bosma et al,[13] Netherlands	2002	830	49-81	Physical exercise, mental and social activities	3	Overall cognitive function	Specific tests for memory, verbal fluency; global cognitive test (MMSE)	Low participation in any activity with cognitive decline
Aartsen et al,[14] Netherlands	2002	2,076	55-85	Everyday activity, including social, experiential, and developmental activities	6	Cognitive test scores	Specific tests for memory, fluid intelligence, and speed, MMSE	No association of any activity with cognition, but information-processing speed with developmental activity
Menec,[15] Canada	2003	1,292	67-95	Social, mental, and productive activities; number of leisure activities	6	Function	Combined physical and mental function index	Greater overall activity, and social and productive activities with better function

Table 4. continued

Zunzunegui et al,[16] Spain	2003	964	>65	Social relations (social network, social integration, and social engagement)	4	Cognitive function, cognitive decline- categorical	Global cognitive functioning (scale including memory and orientation items)	Poor social relations, low participation in social activities, and social disengagement with cognitive decline
Glei et al.,[17] Taiwan	2005	2,384	>=60	Social activities, social network	3-6	Cognitive impairment	Cognitive impairment (# incorrect answers to 5 questions)	Social activities with cognitive impairment, no association for social network
Beland et al.,[18] Spain	2005	1,165	>=65	Social integration, social network (social ties and social engagement)	7	Rate of cognitive decline	Global cognitive function	Social engagement and social integration with cognitive decline, having friends with decline in women only
Saczynski et al.,[19] USA *men only	2006	2,513	46-65 in 1965	Midlife and late- life social engagement - composite index	35	Incident dementia	Clinical consensus diagnosis	Late life but not midlife social engagement with dementia
van Gelder et al.,[20] Europe *men only	2006	1,042	70-89	Marital status and living situation over 5 years	15	Subsequent 10- year rate of cognitive decline	MMSE at multiple time points	Men who lost a partner, who were unmarried, or who started/lived to live alone with worse cognitive decline
Crooks et al.,[21]USA *women only	2008	2,249	78 +	Social networks (Lubben social network scale)	1-5	Incident dementia	Cognitive status, Dementia Questionnaire, medical record review	Larger social network with reduced dementia risk
Ertel et al.,[22] USA	2008	16,638	50+	Social integration	2-6	Rate of memory decline	Episodic memory test	Higher social integration with slower memory decline
Green et al.,[23] USA	2008	874	18+	Social network (size, frequency of contact, and emotional support)	7-11	Cognitive status and change over time	Neuropsychological tests- overall cognition and memory	Cross-sectional but not longitudinal associations

Table 4. continued

Obisesan et al.,[24] USA	2009	5,908	60+	Social network index, cognition	8.5	Death	Overall cognition- Short index of cognitive function	Social network and cognition independently associated with death (no interaction)
Håkansson et al.,[25] Finland	2009	1,449	65-79	Marital status- mid and late life (married/cohabiting, divorced, widowed, never married)	26	Incident cognitive impairment	Main= impairment below 1.5 SD of mean in memory or one other area of cognitive functioning with memory complaints	Married in mid-life with less risk of cognitive impairment. Widowed or divorced highest risk for cognitive impairment
Karlamangla et al.,[26] USA	2009	6,476	60+	Marital status (married, widowed, separated/divorced, never married)	9	Rate of cognitive decline	Neuropsychological tests	Widowed and never-married participants had larger practice effects and faster declines than married.
James et al.,[27] USA	2011	1,138	65+	Late life Social activity (social interaction and participation)	Up to 12	Rate of cognitive decline	Neuropsychological battery	More social activity with less cognitive decline
Stoykova et al.,[28] France	2011	2055	65+	Social functioning-network, participation	20	Baseline cognition and rate of change	Neuropsychological battery and MMSE	Social network with decline (when incident dementia included) no association for "age-related" decline
Roberts et al.,[29] USA	2012	1,450	70-89	Marital status (married, previously married, never married)	3.4	Incident MCI	Clinical diagnosis procedures	Previously married with MCI and aMCI, never married with naMCI
Eisele et al., [30] Germany	2012	2,367	75+	Perceived social support	18 months	Cognitive change	Neuropsychological battery	No association between perceived social support and change in cognition

Appendix B

Table 5. Subject characteristics at baseline by marital status

Characteristic	Married (n=2,891)	Widowed (n=1,142)	Divorced/ Separated (n=616)	Never Married (n=268)	P-value*
Demographics	N(%) unless otherwise noted				
Age (yrs)					<0.001
55-65	562 (19.4)	43 (3.8)	139 (22.6)	58 (21.6)	
65-75	1,313 (45.4)	283 (24.8)	271 (44.0)	115 (42.9)	
75-85	833 (28.8)	479 (41.9)	175 (28.4)	80 (29.9)	
85+	183 (6.3)	337 (29.5)	31 (5.0)	15 (5.6)	
Female	1,595 (55.2)	962 (84.2)	508 (82.5)	211 (78.7)	<0.001
Race					<0.001
Caucasian Non-Hispanic	2,441 (84.4)	829 (72.6)	402 (65.3)	202 (75.4)	
Caucasian- Hispanic	101 (3.5)	44 (3.9)	25 (4.1)	10 (3.7)	
Black-Non-Hispanic	272 (9.4)	252 (22.1)	175 (28.4)	45 (16.8)	
Black -Hispanic	7 (<1)	2 (<1)	2 (<1)	4 (1.5)	
Other- Non-Hispanic	57 (2.0)	11 (<1)	7 (1.1)	6 (2.2)	
Other- Hispanic	13 (<1)	4 (<1)	5 (<1)	1(<1)	
Education (yrs)					<0.001
0-12	504 (17.4)	336 (29.4)	132 (21.4)	28 (10.5)	
13-15	1,289 (44.6)	491 (43.0)	276 (44.8)	103 (38.4)	
16+	1,098 (38.0)	315 (27.6)	208 (33.8)	137 (51.1)	
Reason for coming to ADC					<0.001
Participate in a research study	2,702 (93.5)	1,050 (91.9)	557 (90.4)	215 (80.2)	
Clinical Evaluation	168 (5.8)	78 (6.8)	51 (8.3)	44 (16.4)	
Other/Unknown	21 (<1)	14 (1.2)	8 (1.3)	9 (3.4)	
Health Behaviors (Current or Previous)					
Smoking					0.007
Yes	1,308 (45.2)	488 (42.7)	313 (50.8)	132 (49.3)	
Alcohol abuse					0.001
Yes	79 (2.7)	21 (1.8)	28 (4.6)	15 (5.6)	
Substance abuse					0.001
Yes	23 (<1)	4 (<1)	9 (1.5)	7 (2.6)	
Health Conditions (Present or History of)					
Cardiovascular disease					0.002
Yes	707 (24.5)	328 (28.7)	134 (21.8)	56 (20.9)	
Metabolic condition					0.001
Yes	2,223 (76.9)	940 (82.3)	468 (76.0)	214 (80.0)	
Depression					<0.001
Yes	580 (20.1)	221 (19.4)	191 (30.8)	70 (26.1)	
Psychiatric condition					0.004
Yes	89 (3.1)	26 (2.3)	30 (4.9)	15 (5.6)	
Neurological condition					0.12
Yes	386 (13.4)	125 (11.0)	77 (12.5)	27 (10.1)	
APOE ε4 allele**					0.04
Yes	635 (29.2)	207 (25.2)	131 (32.3)	47 (25.4)	
Cognitive Impairment					
CDR-SB, mean (SD)	0.014 (0.088)	0.022 (0.102)	0.011 (0.072)	0.007 (0.061)	0.005

CDR-SB, Clinical Dementia Rating sum of boxes (range of 0-18, higher signifies more cognitive impairment).
*Calculated using Pearson chi-square test (categorical measures) or Kruskal-Wallis rank test (continuous measures)
**Only assessed for 3,586 (72.9%) of subjects.

Appendix C

Table 6. Subject characteristics at baseline stratified by living situation

Characteristic	Living with Spouse/Partner (n=2,834)	Living with others (n=337)	Living alone (n=1,746)	P-value*
Demographics	N(%) unless otherwise noted			
Age (yrs)				<0.001
55-65	556 (19.6)	53 (15.7)	193 (11.0)	
65-75	1,292 (45.6)	119 (35.3)	571 (32.7)	
75-85	811 (28.6)	100 (29.7)	656 (37.6)	
85+	175 (6.2)	65(19.3)	326 (18.7)	
Female	1,563 (55.2)	284 (84.3)	1,429 (81.8)	<0.001
Race				<0.001
Caucasian Non-Hispanic	2,398 (84.6)	183 (54.3)	1,293 (74.1)	
Caucasian- Hispanic	97 (3.4)	30 (8.9)	53 (3.0)	
Black-Non-Hispanic	267 (9.4)	113 (33.5)	364 (20.9)	
Black -Hispanic	5 (<1)	2 (<1)	8 (<1)	
Other- Non-Hispanic	54 (1.9)	5 (1.5)	22 (1.3)	
Other- Hispanic	13 (<1)	4 (1.2)	6 (<1)	
Education (yrs)				<0.001
0-12	492 (17.4)	107 (31.8)	401 (23.0)	
13-15	1,260 (44.5)	138 (41.0)	761(43.6)	
16+	1,082 (38.2)	92 (27.3)	584 (33.5)	
Reason for coming to ADC				<0.001
Participate in a research study	2,650 (93.5)	314 (93.2)	1,560 (89.4)	
Clinical Evaluation	162 (5.7)	20 (5.9)	159 (9.1)	
Other/Unknown	22 (<1)	3 (<1)	27 (1.6)	
Health Behaviors (Current or Previous)				
Smoking				0.18
Yes	1,275 (45.0)	143 (42.4)	823 (47.1)	
Alcohol abuse				0.74
Yes	78 (2.8)	55 (3.2)	10 (3.0)	
Substance abuse				0.41
Yes	22 (<1)	16 (<1)	5 (1.5)	
Health Conditions (Present or History of)				
Cardiovascular disease				0.009
Yes	686 (24.2)	67 (19.9)	472 (27.0)	
Metabolic condition				0.007
Yes	2,173 (76.7)	277 (82.2)	1,395 (79.9)	
Depression				0.02
Yes	572 (20.2)	76 (22.6)	413 (23.7)	
Psychiatric condition				0.77
Yes	89 (3.1)	13 (3.9)	58 (3.3)	
Neurological condition				0.12
Yes	378 (13.3)	39 (11.6)	198 (11.3)	
APOE ε4 allele**				0.006
Yes	625 (29.3)	82 (35.0)	313 (25.7)	
Cognitive Impairment				0.26
CDR-SB, mean (SD)	0.013 (0.087)	0.018 (0.093)	0.017 (0.090)	

CDR-SB, Clinical Dementia Rating sum of boxes (range of 0-18, higher signifies more cognitive impairment).
*Calculated using Pearson chi-square test (categorical measures) or Kruskal-Wallis rank test (continuous measures)
**Only assessed for 3,586 (72.9%) of subjects.